Studies on the Mechanism of 1,3-Butadiene-induced Leukemogenesis: The Potential Role of Endogenous Murine Leukemia Virus

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Previous studies have revealed marked differences in the incidence of leukemia between rats and mice exposed to 1,3-butadiene that do not appear to be readily explained on the basis of pharmacokinetics or metabolism. Chronic exposure to 1,3-butadiene results in a high incidence of thymic lymphoma in B6C3F$_1$ mice that is not observed in Sprague-Dawley rats. Studies at the Chemical Industry Institute of Toxicology have focused on evaluating the potential of endogenous ecotropic retroviral background to influence susceptibility to 1,3-butadiene leukemogenesis. These studies have compared the pathogenesis and incidence of thymic lymphoma between B6C3F$_1$ and NIH Swiss mice. Proviral ecotropic sequences are truncated in the NIH Swiss mouse, and the virus is not expressed. Chronic exposure to 1,3-butadiene (1250 ppm) for up to 1 year resulted in a fourfold difference in the incidence of thymic lymphoma between B6C3F$_1$ and NIH Swiss mice. These results provide presumptive evidence for retrovirus involvement since NIH Swiss mice lack ecotropic viruses and appear to be relatively resistant to induction of lymphoma by 1,3-butadiene. Other explanations appear to be less likely in light of the fact that target organ toxicity has been determined to be virtually identical between the two strains during the preleukemic phase of 1,3-butadiene exposure.

Introduction

One of the most intriguing aspects of 1,3-butadiene toxicity is the marked species difference in its carcinogenic potency—a central factor being the remarkably high incidence of thymic leukemia/lymphoma encountered in B6C3F$_1$ mice but not rats (*1–2*). The importance of elucidating the mechanisms of 1,3-butadiene leukemogenesis in the mouse is underscored by evidence suggesting that there may be an increased risk of lymphatic and hematopoietic neoplasms in 1,3-butadiene-exposed populations (*3–6*). Mechanisms most likely to contribute to major species or strain differences in chemically induced leukemogenesis are metabolism or retroviral background. Quantitative differences in the rates of 1,3-butadiene metabolism between rats and mice have been described; however, it is unlikely these can account for the observed differences in susceptibility to 1,3-butadiene-leukemogenesis because comparable tissue metabolite concentrations have been demonstrated in both species over the range of 1,3-butadiene exposure concentrations that were employed (*7*). Be-

cause of the frequent association of endogenous retrovirus with spontaneous lymphomas in the mouse, a major focus of our studies has been to determine if endogenous retroviral background could potentially influence 1,3-butadiene-leukemogenesis.

Endogenous Retroviruses and Murine Leukemogenesis

Laboratory mice possess a number of proviral genes that code for retroviruses or retroviruslike elements that have been collectively termed murine leukemia viruses (MuLV). Without modification, endogenous MuLV sequences have not been directly associated with pathology (*8*). All leukemogenic MuLV characterized to date are recombinants, the formation of which has not been observed in the absence of complete ecotropic sequences (*9–11*). Therefore, it has been proposed that leukemogenesis must be preceded by the generation of recombinant virus sequences, and that both ecotropic and recombinant viruses may play critical roles in strain-specific viral leukemogenesis (*12*).

The role of endogenous retrovirus in the etiology of chemically induced murine leukemogenesis is presently not understood. MuLV are known to produce a high

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incidence of spontaneous leukemias in specific mouse strains such as the AKR and C58 (10,13). Leukemogenic retroviruses have been isolated from radiation-induced leukemias in certain strains including the parent strains of the B6C3F$_1$ hybrid mouse (14–20), and there is evidence that ecotropic and recombinant MuLV play critical roles in strain-specific spontaneous leukemogenesis (12). In spontaneous leukemias of the mouse, the role for MuLV is definitive (8); nevertheless, contradictory findings have been encountered in chemical leukemogenesis in certain strains. A filterable leukemogenic agent has been isolated from thymic lymphomas from CFW/D mice induced by 7,12-dimethyl-benz[a]anthracene or 3-methylcholanthrene (MCA) (21). However, others have been unable to establish a viral etiology in MCA-induced lymphomas in RF/J mice (22,23).

Although the mechanisms of leukemogenesis are potentially complex, the number of practical possibilities involving ecotropic retrovirus can be reduced to a small number. These alternative scenarios are a) retroviruses are generated that are leukemogenic; 1,3-butadiene is not; b) both altered retroviruses and 1,3-butadiene exposure are independently leukemogenic (additive co-carcinogenesis); c) ecotropic retrovirus sequences are necessary but not frankly leukemogenic by themselves (facilitative co-carcinogenesis); d) ecotropic retroviruses are activated but play no role in 1,3-butadiene-induced leukemogenesis; and e) ecotropic retroviruses are not activated and play no role in 1,3-butadiene-induced leukemogenesis. These alternatives were initially evaluated in a series of comparative studies using two different strains of mice, the B6C3F$_1$ and the NIH Swiss. The B6C3F$_1$ hybrid was chosen because it has been shown to develop a high incidence of thymic lymphoma following 1,3-butadiene exposure. The NIH Swiss mouse was chosen because it does not possess intact endogenous ecotropic retrovirus sequences, does not express ecotropic retroviruses, and rarely expresses any type of endogenous retrovirus (24,25).

Comparative Studies on the Pathogenesis of 1,3-Butadiene-induced Leukemia/Lymphoma

A predominant feature of most leukemias in man and experimental animals is the involvement of the hematopoietic stem cell as a common target in the leukemogenic process. Furthermore, bone marrow injury plays an essential role in radiation-induced leukemia/lymphoma (19,26,27). Therefore, it is not surprising that the bone marrow is the primary target organ for 1,3-butadiene toxicity (28). Subchronic exposure of B6C3F$_1$ mice to 1250 ppm for 3 to 24 weeks resulted in a macrocytic anemia with alterations reminiscent of those encountered in megaloblasic anemia in man. These changes were accompanied by alterations in bone marrow stem cell proliferation and differentiation (29). In addition, 1,3-butadiene exposure resulted in a marked increase in the number of micronuclei in bone marrow and the peripheral circulation (Fig. 1) and increases in the frequency of chromosomal aberrations of the chromatid type in B6C3F$_1$ mice (28,30). Since no extranumerary chromosomes were noted, it was concluded that the mechanism of micronuclei formation following 1,3-butadiene exposure is most likely due to chromatid breaks rather than mitotic spindle events.

A striking finding was the increase in recoverable ecotropic MuLV from bone marrow, thymus, and spleen of B6C3F$_1$ mice (31). This was most pronounced in the spleen and amounted to a 1 to 10×10^3 increase in the

FIGURE 1. Micronuclei in bone marrow cells from B6C3F$_1$, mouse exposed to 1,3-butadiene (1250 ppm) for 6 weeks. (Bone marrow smear; Wright stain; ×630).
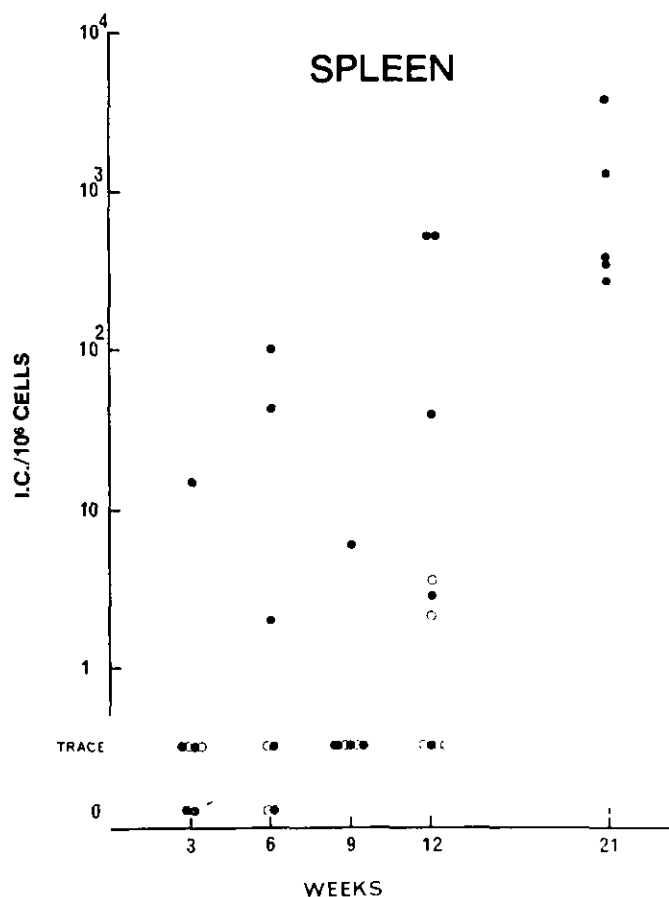
FIGURE 2. Ecotropic retrovirus expression in spleens of B6C3F$_1$ mice. 1,3-Butadiene-exposed (●); control (○); X-axis, duration of exposure; Y-axis, infectious centers/10^6 cells. Trace: virus detectable but only after multiple passages. 0: no virus detectable after multiple passages. Figure modified from Irons et al. (*31*).

production of ecotropic MuLV during the preleukemic phase of 1,3-butadiene exposure (Fig. 2). Additional experiments revealed that the mechanism of viral activation probably involves *de novo* increases in selective ecotropic MuLV replication in individual cells, rather than alterations in the ability of the mice to restrict virus movement.

Exposure of NIH Swiss mice to 1,3-butadiene under identical conditions resulted in a macrocytic anemia, increases in circulating micronuclei, as well as micronuclei and chromosomal abnormalities in bone marrow cells (*30,32*). In each case the changes were qualitatively and quantitatively indistinguishable from those described in 1,3-butadiene-exposed B6C3F$_1$ mice. The principle difference between the two strains was the inability to recover MuLV of any type from tissues of NIH Swiss mice (*31*). These findings are summarized in Table 1.

Comparative Lymphoma/Leukemia Incidence Study

The incidence of thymic lymphoma/leukemia in B6C3F$_1$ mice chronically exposed to 1250 ppm 1,3-butadiene for 1 year was 57% (*33*). This is nearly identical to the 60% incidence previously reported by Huff et al. (*1*). These presented predominantly as mediastinal masses, the thymus showing primary involvement in the majority of cases (Fig. 3). A single lymphoid tumor was encountered in the control group. In addition, a significant incidence of thymic lymphoma (21%) was also encountered in B6C3F$_1$ mice exposed for 12 weeks and held for 1 year (Fig. 4). Thymic lymphoma were characterized as aggressive lymphoid tumors, consisting of highly proliferative uniform populations of well-differentiated lymphoblasts, with frequent involvement of adjacent and distant tissues including lungs, heart, spleen, lymph nodes, liver, and kidney. Although the incidence of thymic lymphoma was higher in animals exposed for the full year, no differences in the latency or time-to-tumor were noted between the two groups (Fig. 5). Cytofluorometric analysis revealed the thymic lymphoma to be of T-cell origin and to exhibit variable but elevated surface expression of MuLV *env* antigens (Fig. 6). In contrast, NIH Swiss mice exposed to 1,3-butadiene for 52 weeks presented with a much lower incidence of thymic lymphoma (14%) (Fig. 7). These tumors were morphologically similar to those encountered in B6C3F$_1$ mice and expressed T-cell but no MuLV *env* surface antigens.

Table 1. Comparative hematology of B6C3F$_1$ and NIH Swiss mice following exposure to 1,3-butadiene.[a]

Peripheral blood	B6C3F$_1$			NIH Swiss		
	Treated	Control	(%Δ)	Treated	Control	(%Δ)
White blood cells × 10^3	1.61	2.34	− 31*	1.60	2.13	− 25*
Hematocrit	36.9	43.3	− 15	32.5	40.0	− 21
Hemoglobin	12.8	14.9	− 14	11.4	13.8	− 17
Red blood cells × 10^6 RBC	6.55	8.9	− 26	5.95	7.93	− 25
Mean corpuscular volume	56.2	48.7	+ 15	50.5	54.6	+ 8
Reticulocytes/10^3 RBC	50.8	31.5	+ 61*	46.7	50.6	+ 8*
Micronuclei/10^3 RBC	26.5	5.0	+ 530	26.4	3.4	+ 776
Bone marrow cellularity × 10^6	19.7	21.9	− 10	19.3	26.2	− 26
Chromatid abberations	47	2		33	4	

[a]All parameters measured after 6 weeks of exposure to 1250 ppm except chromatid aberrations which were measured 24 hr after a single 6-hr exposure. Table is taken from Irons et al. (*33*).
*Difference not significant at $p < 0.05$.

FIGURE 3. Photomicrograph of thymic lymphoma from 1,3-butadiene-treated B6C3F$_1$ mouse. Tumors consist of rapidly proliferating well-differentiated blast cells. (H&E paraffin; ×630).
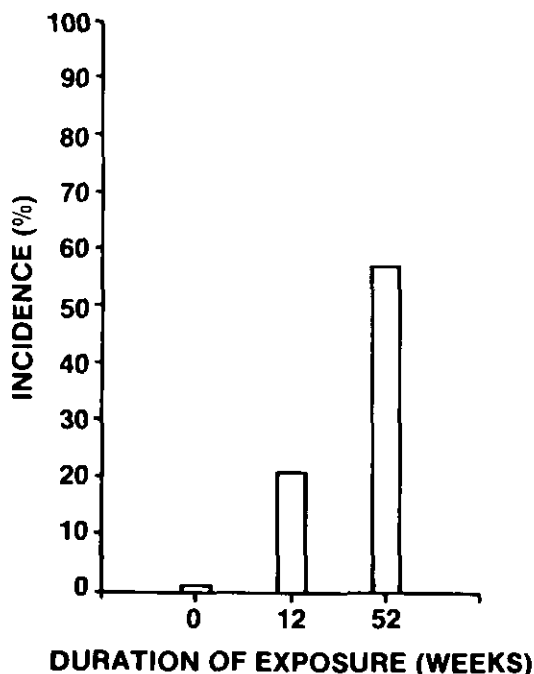

FIGURE 4. Incidence of thymic lymphoma in B6C3F$_1$ mice at 1 year following exposure to 1,3-butadiene (1250 ppm) for 0, 12, or 52 weeks. Figure taken from Irons et al. (33).
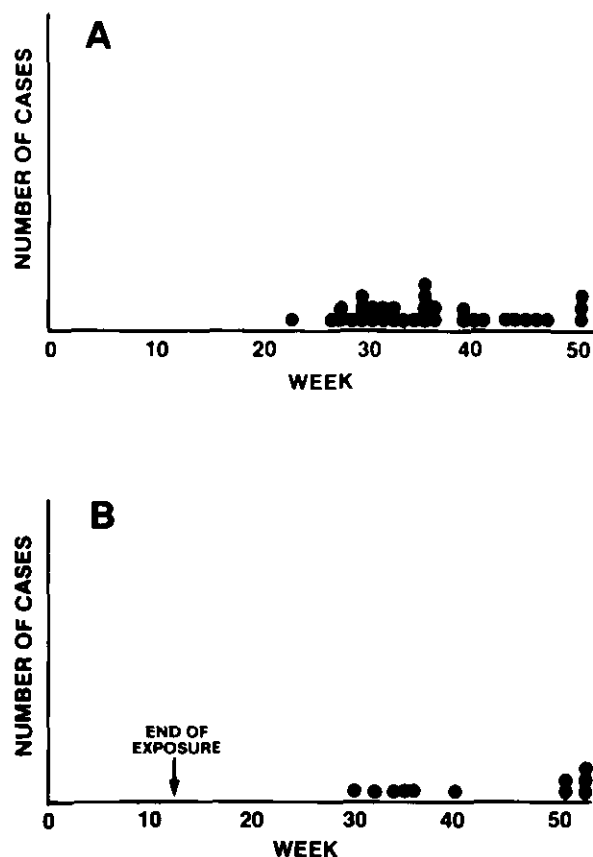
FIGURE 5. Chronology of thymic lymphomas in B6C3F$_1$ mice chronically exposed to 1,3-butadiene (11250 ppm) for (A) 12 or (B) 52 weeks. Figure taken from Irons et al. (33).

Discussion

Understanding the mechanism of thymic lymphoma in 1,3-butadiene-exposed mice is of major importance, especially when viewed in light of the possibility that 1,3-butadiene exposure in man may be associated with an increased incidence of similar neoplasms. Although the data are incompatible with the hypothesis that leukemogenic MuLV are entirely responsible for the incidence of thymic lymphoma, the described studies suggest that ecotropic MuLV may influence the incidence of 1,3-butadiene-induced lymphoma in the mouse. A major difference between NIH Swiss and B6C3F$_1$ mice is their respective ecotropic retroviral background, and the prospect that differences in leukemia incidence could be explained by strain-specific metabolism or bioactivation of 1,3-butadiene remains unlikely, since, with the exception of the increased recovery of ecotropic retrovirus from tissues of B6C3F$_1$ mice, target organ toxicity in the two strains is qualitatively and quantitatively identical following 1,3-butadiene exposure. Therefore, ecotropic retroviral background remains the most likely explanation for the marked difference in lymphoma incidence encountered in these mice following 1,3-butadiene exposure. It is possible that two additive mechanisms,
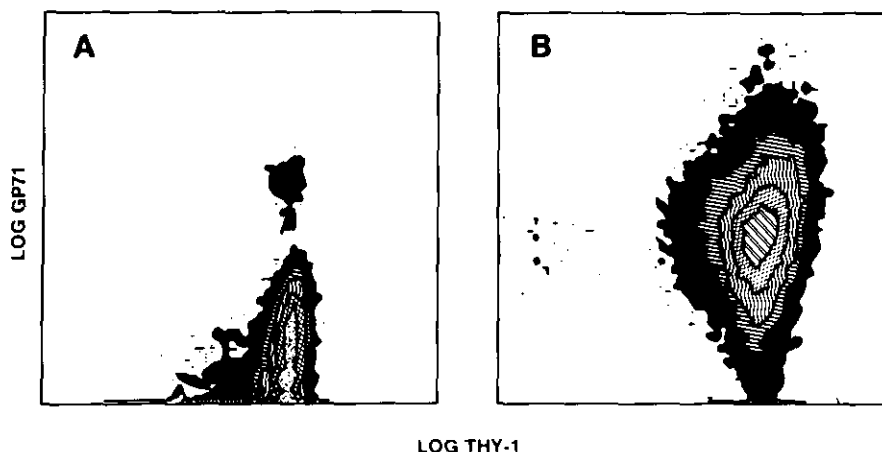
FIGURE 6. Flow cytometric contour projections of normal thymic *(A)* and respective leukemia cells *(B)* showing dual expression of MuLV *env* and Thy 1.2 antigens. The leukemia shown exhibited the lowest amounts of *env* expression of seven isolated and characterized. Figure taken from Irons et al. *(33)*.
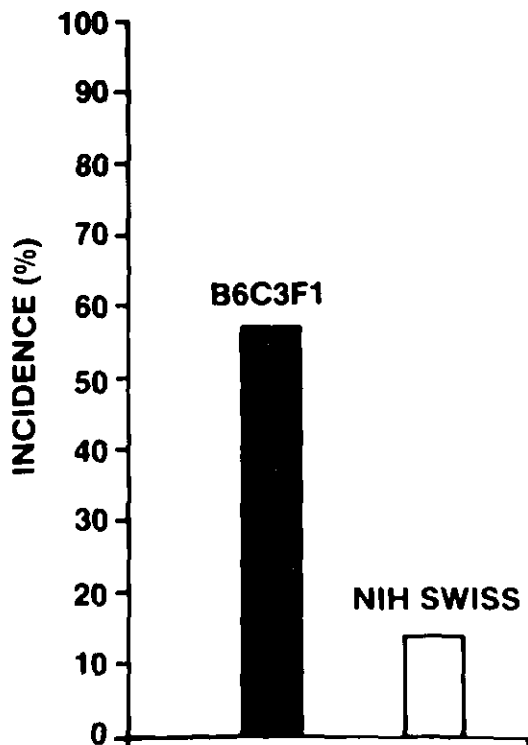

FIGURE 7. Comparative incidence of thymic lymphoma in B6C3F$_1$ and NIH Swiss mice chronically exposed to 1,3-butadiene (1250 ppm) for 1 year. Taken from Irons et al. *(33)*.

one requiring retrovirus and one not, account for the increased incidence of lymphoma in the B6C3F$_1$ mouse. Alternatively, retrovirus may play a synergistic role in 1,3-butadiene-induced lymphoma. Transformation of leukemia virus-infected rat or mouse embryo cells by chemicals has been demonstrated under conditions where neither virus infection nor chemical treatment alone resulted in transformation *(34–38)*.

Experiments that will be necessary to provide definitive confirmation of the role of endogenous ecotropic MuLV in 1,3-butadiene leukemogenesis in the mouse include: determination of the leukemogenicity of retroviral isolates from 1,3-butadiene-induced lymphomas and a comparison of susceptibility to 1,3-butadiene-leukemogenesis between congenic mouse strains differing only at the ecotropic retrovirus locus. Moreover, the mechanism of 1,3-butadiene-induced *de novo* activation of MuLV in mouse cells needs to be explored in order to determine the relevance of this model, if any, to the potential for 1,3-butadiene to alter the expression, replication, or latency of retroviruses in other species. Evidence strongly suggests that environmental or occupational factors influence transformation in HTLV-1-associated neoplasms in man *(39)*, and chemical alterations in HTLV-1 expression in human cells in culture have been reported *(40–42)*.

It is possible that the B6C3F$_1$ hybrid may not prove to be the most appropriate animal model for extrapolation of the risk of 1,3-butadiene leukemogenesis to the general human population. If a definitive role for MuLV is established, a strain that does not express ecotropic MuLV may be more appropriate. Independently, if similarities exist between the effects of 1,3-butadiene or its metabolites on the expression of retroviruses in mouse and human cells, then the B6C3F$_1$ mouse may be appropriate for modeling at least one human population at potential risk, e.g., human T-lymphotrophic virus type-1-infected individuals. Furthermore, if the biology of human retroviruses is altered following 1,3-butadiene exposure, then other potential human health risks, including but not limited to leukemia, need to be evaluated.

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